CLAIMS

1. A continuous method of forming particles comprising the following steps:

(d) providing an aqueous solution comprising coprecipitant molecules and bioactive molecules, each coprecipitant molecule substantially having a molecular weight of less than 4kDa, wherein the aqueous solution is capable of forming a coprecipitate which comprises the coprecipitant and bioactive molecules with a melting point of above about 90°C;

(e) rapidly admixing the bioactive molecule/coprecipitant molecule solution with a greater volume of a substantially water miscible organic solvent such that the coprecipitant and bioactive molecules coprecipitate from solution forming said particles; and

(f) optionally isolating the particles from the organic solvent.

2. A method according to claim 1 wherein the bioactive molecule is provided as a solid such as a powder, which is to be dissolved in an aqueous solution of coprecipitant.

3. A method according to claim 1 wherein the bioactive molecule is in a solution or suspension prior to mixing with an aqueous solution of coprecipitant.

4. A method according to any preceding claim wherein following mixing with the bioactive molecule the coprecipitant will be at between about 5 and 100 % or

between about 20 and 80 % of its aqueous saturation solubility.

5. A method according to any preceding claim wherein the coprecipitant is present in the aqueous solution at a concentration of less than about 150 mg/ml or less than about 80 mg/ml.

6. A method according to any preceding claim wherein the coprecipitant is non-hygroscopic.

7. A method according to any preceding claim wherein the bioactive molecule loading, such as protein loading in the particles is defined by setting the concentration of the bioactive molecule in the aqueous phase.

8. A method according to any preceding claim wherein the bioactive molecule loading, such as protein loading in the particles is defined by setting the concentration of the coprecipitant in the aqueous phase.

9. A method according to any preceding claim wherein the coprecipitant has a substantially lower solubility in the miscible organic solvent than in the aqueous solution.

10. A method according to any preceding claim wherein an excess of fully water miscible organic solvent is such that the final water content of the solvent/aqueous solution is generally less than about 30 vol%, less than about 10-20 vol% or less than about 8 vol%.

11. A method according to any preceding claim wherein the water miscible organic solvent is selected from any

of the following: methanol; ethanol; propan-1-ol; propan-2-ol; acetone, ethyl lactate, tetrahydrofuran, 2-methyl-2,4-pentanediol, 1,5-pentanediol, and various size polyethylene glycol (PEGS) and polyols; or any combination thereof.

12. A method according to any preceding claim wherein the organic solvent is pre-saturated with the bioactive molecule and/or coprecipitate to ensure that on addition and mixing of the aqueous solution the two components precipitate out together.

13. A method according to any preceding claim wherein the aqueous phase is added slowly to a large excess of the solvent phase and a mixing process that is turbulent or near turbulent is used.

14. A method according to any preceding claim wherein the aqueous solution is added to organic solvent as a continual stream, spray or mist.

15. A method according to any preceding claim wherein a water miscible organic solvent or mixture of solvents is continuously flowed and mixed with a slower flowing aqueous stream comprising a bioactive molecule and coprecipitant solution producing a combined output flow that contains suspended bioactive molecule coated microcrystal particles.

16. A method according to claim 15 wherein the solvent and aqueous flows are continuously pumped at different rates through tubing and combined in a static mixing device such as a T junction or Y junction.

17. A method according to claim 15 wherein the solvent and aqueous flows are continuously pumped at different rates through tubing and combined in a dynamic mixing device such as a solvent gradient mixer or a modified solvent gradient mixer.

18. A method according to claim 17 wherein the dwell time in the mixing device is less than about 0.2 minutes, less than about 0.05 minutes or less than about 0.02 minutes.

19. A method according to any of claims 15 to 18 wherein the solvent flow and aqueous flow are independently sterilised prior to mixing by pumping them through separate sterile filters.

20. A method according to any of claims 15 to 19 wherein one pump continuously delivers aqueous solution containing the coprecipitant and the bioactive molecule, a second pump delivers a coprecipitant saturated solvent phase and optionally further pumps are used to provide other components such as a particle coating material.

21. A method according to any of claims 16 to 20 wherein the pumps used are high performance pumps that can deliver precise flow rates at high pressure such as HPLC pumps.

22. A method according to any of claims 16 to 21 wherein the solvent is pumped into the mixing device at a flow-rate 4 to 100 times faster than the aqueous flow-rate.

23. A method according to any of claims 16 to 22 wherein pump-heads and the mixing device are made of material

which exhibit low fouling by biomolecules and which can be easily cleaned and sterilised such as stainless steel.

24. A method according to any preceding claim wherein the aqueous solution is delivered at flow rates between about 0.1 ml/min and 20 ml/min and the solvent is delivered at between about 2 ml/min and 200 ml/min.

25. A method according to any preceding claim wherein upon admixing the bioactive molecule/coprecipitant solution to the excess of the water miscible organic solvent, precipitation of the bioactive and coprecipitant occurs substantially instantaneously.

26. A method according to any preceding claim wherein following coprecipitation the solvent in which the particles is suspended is exchanged for a different one by decanting and rinsing the particles without drying.

27. A method according to any preceding claim wherein a suspension of particles is concentrated in a batch or continuous process to give a higher solid content prior to drying.

28. A method according to any preceding claim wherein the coprecipitate is subjected to batch or continuous centrifugation and/or filtration in order to rapidly recover the precipitated particles.

29. A method according to any preceding claim wherein concentration of a suspension of particles is achieved by batch or continuous filtration or centrifugation or by allowing the coprecipitate to settle and decanting of excess solvent.

30. A method according to any preceding claim wherein batch or continuous drying procedures such as air drying, vacuum drying or fluidised bed drying are used to evaporate any residual solvent to leave substantially solvent free particles.

31. A method according to any of claims 1 to 29 wherein solvent is removed from the particles in a batch or continuous process using a supercritical fluid such as supercritical carbon dioxide.

32. A method according to any of claims 1 to 29 wherein solvent is removed from a suspension of bioactive molecule coated microcrystals in a high pressure chamber by flowing high pressure fluid carbon dioxide at, near or above the critical point through the suspension and wherein once the solvent is substantially removed the pressure is lowered while at a temperature above the critical temperature of carbon dioxide.

33. A method according to any preceding claim wherein for pharmaceutical applications dry precipitated particles are introduced into a sterile delivery device or vial under sterile conditions prior to use, or the particles are transferred into a sterile delivery device or vial as a suspension in solvent under sterile conditions.

34. A method according to any preceding claim wherein the dosage is varied by varying the percentage weight of bioactive molecule per particle from below about 0.1 wt% up to about 50 wt%.

35. Particles as formed according to any of claims 1 to 33.

36. Particles obtainable by:

(a) providing an aqueous solution comprising coprecipitant molecules and bioactive molecules, each coprecipitant molecule substantially having a molecular weight of less than 4kDa, wherein the aqueous solution is capable of forming a coprecipitate which comprises the coprecipitant and bioactive molecules with a melting point of above about 90°C;

(b) rapidly admixing the bioactive molecule/coprecipitant molecule solution with a greater volume of a substantially water miscible organic solvent such that the coprecipitant and bioactive molecules coprecipitate from solution forming said particles; and

(c) optionally isolating the particles from the organic solvent.

37. A pharmaceutical formulation comprising particles wherein the particles comprise:

(c) a substantially non-hygroscopic inner crystalline core comprising coprecipitant molecules wherein said coprecipitant molecules have a molecular weight of less than 4kDa; and

(d) an outer coating comprising one or more bioactive molecules

wherein the particles have been formed in a single step by coprecipitating said core forming coprecipitant molecules and said bioactive molecule(s) together and

wherein the particles have a melting point of above about 90°C.

38. A pharmaceutical formulation according to claim 37 wherein the particles are formed by a batch method wherein a bioactive molecule/coprecipitant molecule solution is added to an excess of a substantially water miscible organic solvent.

39. A pharmaceutical formulation according to claim 37 wherein the particles are formed by a continuous method as defined in claims 1 to 36.

40. A pharmaceutical formulation according to any of claims 37 to 39 wherein the crystalline core shows X-ray diffraction.

41. A pharmaceutical formulation according to any of claims 37 to 40 wherein the pharmaceutical formulation comprises non-spherical particles with a narrow size distribution such as a Span of less than about 5, less than about 2 or less than about 1.5.

42. A pharmaceutical formulation according to any of claims 37 to 41 wherein the particles have a maximum cross-sectional dimension of less than about 80μm, less than about 50μm or less than about 20μm.

43. A pharmaceutical formulation according to any of claims 36 to 41 wherein the molecules making up the crystalline core have a molecular weight of less than about 2kDa, less than about 1kDa or less than about 500 Daltons.

44. A pharmaceutical formulation according to any of claims 37 to 43 wherein the molecules forming the crystalline core have a solubility in water of less than about 150 mg/ml or less than about 80 mg/ml.

45. A pharmaceutical formulation according to any of claims 37 to 44 wherein the molecules which make up the crystalline core are selected from any of the following: amino acids, zwitterions, peptides, sugars, buffer components, water soluble drugs, organic and inorganic salts, compounds that form strongly hydrogen bonded lattices or derivatives or any combinations thereof.

46. A pharmaceutical formulation according to any of claims 37 to 45 wherein amino acids form the crystalline core and are used either in pure enantiomeric form or as a racemate mixture.

47. A pharmaceutical formulation according to claim 46 wherein the amino acids suitable for forming the crystalline core are: glutamine, histidine, serine, methionine, isoleucine or valine.

48. A pharmaceutical formulation according to any of claims 37 to 46 wherein bioactive molecules forming a coating on the crystalline core are selected from any molecule capable of producing a therapeutic effect such as an active pharmaceutical ingredient (API).

49. A pharmaceutical formulation according to any of claims 37 to 48 wherein the coating of bioactive molecules also comprises excipients commonly used in pharmaceutical formulations such as stabilizers,

surfactants, isotonicity modifiers and pH/buffering agents.

50. A pharmaceutical formulation according to any of claims 37 to 49 wherein the bioactive molecules comprise: any drug, peptide, polypeptide, protein, nucleic acid, sugar, vaccine component, or any derivative thereof or any combination which produces a therapeutic effect.

51. A pharmaceutical formulation according to any of claims 37 to 50 wherein the bioactive molecules comprise: anti-inflammatories, anti-cancer agents, anti-psychotic agents, anti-bacterial agents, anti-fungal agents; natural or unnatural peptides; proteins such as insulin, α1-antitrypsin, α-chymotrypsin, albumin, interferons, antibodies; nucleic acids such as fragments of genes, DNA from natural sources or synthetic oligonucleotides, anti-sense nucleotides and RNA; and sugars such as any mono-, di- or polysaccharides; and plasmids.

52. A pharmaceutical formulation according to any of claims 37 to 51 wherein vaccine coating components include antigenic components of a disease causing agent, such as a bacterium or virus, such as diptheria toxoid and/or tetanus toxoid.

53. A pharmaceutical formulation according to claim 52 wherein the vaccine components are sub-unit, attenuated or inactivated organism vaccines such as diphtheria, tetanus, polio, pertussus and hepatitis A, B and C, HIV, rabies and influenza.

54. A pharmaceutical formulation according to claim 52 wherein the vaccine is diphtheria taxoid coated D,L-valine or L-glutamine crystals.

55. A pharmaceutical formulation according to any of claims 37 to 54 wherein the particles are also applicable to administration of polysaccharides linked to proteins such as HiB (haemopholis influenza B) and pneumococcal vaccines and live virus vaccines, such as mumps, measles, rubella and modern flu vaccine components such as MV A vectored influenza vaccine.

56. A pharmaceutical formulation according to any of claims 37 to 55 wherein vaccine component coated micro-crystals are used for formulation of vaccines developed for cancers, especially human cancers, including melanomas, skin cancer, lung cancer, breast cancer, colon cancer and other cancers.

57. A pharmaceutical formulation according to any of claims 37 to 56 wherein the particles are selected from the following: a crystalline core of valine and a coating of insulin; a crystalline core of glycine and a coating of antitrypsin, a crystalline core of Na glutamate and a coating of insulin; a crystalline core of methionine and a coating of insulin; a crystalline core of alanine and a coating of insulin; a crystalline core of valine and a coating of insulin; a crystalline core of histidine and a coating of insulin; a crystalline core of glycine and a coating of α - antitrypsin; a crystalline core of glutamine and a coating of albumin: a crystalline core of valine and a coating of oligonucleotides DQA-HEX; a crystalline core of valine and a coating of α1-antitrypsin with a further anti-oxidant outer coating of

N-acetyl cystein; a crystalline core of valine and a coating of ovalbumin; a crystalline core of glutamine and a coating of ovalbumin, a crystalline core of valine and a coating of diptheria taxoid; a crystalline core of glutamine and a coating of diptheria taxoid; a crystalline core of valine and a coating of diptheria taxoid; a crystalline core of the glutamine and a coating of tetanus taxoid; a crystalline core of the valine and a coating of a mixture of diptheria taxoid and tetanus taxoid; a crystalline core of glutamine and a coating of a mixture of diptheria taxoid and tetanus taxoid.

58. A pharmaceutical formulation according to any of claims 37 to 57 composed of individual bioactive molecule coated microcrystals with a narrow size distribution that exhibit substantially the same morphology or crystal-shape.

59. A pharmaceutical formulation according to any of claims 37 to 58 where the particles have a maximum cross-sectional dimension of between about 0.5 and 20 microns.

60. A pharmaceutical formulation according to any of claims 37 to 59 that contains spherical aggregates made up of similar sized microcrystals wherein the maximum diameter of the spherical aggregation is less than about 50 microns, or less than about 20 microns.

61. A pharmaceutical formulation according to claim 60 wherein the microcrystals have a needle or rod-like morphology.

62. A pharmaceutical formulation according to any of claims 37 to 61 wherein the bioactive molecules make up

between about 0.1 wt% and 50 wt% or about 1 wt% and 40 wt% of each coated microcrystal particle.

63. A pharmaceutical formulation according to any of claims 37 to 62 wherein water is adsorbed substantially reversibly on equilibration up to a relative humidity of 80%.

64. A pharmaceutical formulation according to claim 63 wherein a reconstitution less than about 5% or less than about 1% of aggregated molecules are observed by size exclusion chromatography.

65. A pharmaceutical formulation according to any of claims 37 to 64 wherein first and second water sorption isotherms measured up to a relative relative humidity of 80% are substantially the same.

66. A pharmaceutical formulation according to any of claims 37 to 65 wherein a first two dynamic water vapour sorption curves measured up to a relative humidity of 80% are substantially the same.

67. A pharmaceutical formulation according to any of claims 37 to 66 in which the particles retain substantially the same crystallinity following equilibration to a relative humidity of up to about 60% or up to about 80%.

68. A pharmaceutical formulation according to any of claims 37 to 67 in which the particles retain substantially the same shape and size following equilibration at a relative humidity of up to about 60% or up to about 80%.

69. A pharmaceutical formulation according to any of claims 37 to 68 in which the particles retain substantially the same free flowing properties following equilibrium at a relative humidity of up to about 60% or up to about 80%.

70. A pharmaceutical formulation according to any of claims 37 to 69 wherein following exposure to temperature of up to 60°C for 1 week and reconstitution in aqueous solution the bioactive molecule retains a biological activity substantially similar to that of a freshly prepared formulation.

71. A pharmaceutical formulation according to any of claims 37 to 70 wherein following exposure to temperatures of up to 60°C for 1 week and reconstitution in aqueous solution the bioactive molecule retains a biological activity substantially similar to that of a freshly prepared formulation.

72. A pharmaceutical formulation according to any of claims 37 to 71 wherein the crystalline core material of the non-hygroscopic coated particles will absorb less than 5 wt% of water or less than 0.5 wt% at relative humidities of up to 80%.

73. A pharmaceutical formulation according to any of claims 37 to 72 wherein on reconstitution in aqueous solution the bioactive molecule has a biological activity substantially similar to that of a freshly prepared solution of it's native counterpart.

74. A pharmaceutical formulation according to any of claims 37 to 73 wherein the bioactive molecule retains greater than about 50% of biological activity after storage at 25°C for 6 months or else greater than about 80% biological activity or else greater than about 95% biological activity as indicated by reconstitution of the bioactive molecule in aqueous solution and comparison with a freshly prepared solution of it's native counterpart.

75. A pharmaceutical formulation according to any of claims 37 to 74 that on reconstitution into an aqueous solution substantially fully dissolves in less than about 2 minutes or less than about 30 seconds to give a clear solution of low turbidity with a clarity better than about 15 FNU or better than about 6 FNU.

76. A pharmaceutical formulation according to any of claims 37 to 75 wherein the formulation is delivered to a recipient by parenteral, pulmonary, nasal, sublingual, intravenous, rectal, vaginal, intra-anal or oral administration.

77. A pharmaceutical formulation according to any of claims 37 to 76 comprising a dry powder of bioactive molecule coated microcrystals with a bulk density of less than about 0.3g/ml or less than about 0.1 g/ml.

78. A pharmaceutical formulation for pulmonary delivery comprising particles according to any of claims 1 to 36.

79. A pharmaceutical formulation according to claim 78 wherein bioactive molecules suitable for the formation of pulmonary pharmaceutical formulations include any of the

following: therapeutic proteins such as insulin, α1-antitrypsin, interferons; antibodies and antibody fragments and derivatives; therapeutic peptides and hormones; synthetic and natural DNA including DNA based medicines; enzymes; vaccine components; antibiotics; pain-killers; water-soluble drugs; water-sensitive drugs; lipids and surfactants; polysaccharides; or any combination or derivatives thereof.

80. A pharmaceutical formulation according to any of claims 78 or 79 wherein the pulmonary formulation comprising particles are used directly in an inhaler device to provide high emitted doses and high fine particle fractions.

81. A pharmaceutical formulation according to claim 80 wherein the fine particle fractions are substantially not altered by exposure to high humidity such as about 80 - 90% humidity.

82. A pharmaceutical formulation according to any of claims 76 to 81 wherein emitted doses measured in a MSLI (stages 1-5) are greater than about 70%.

83. A pharmaceutical formulation according to any of claims 76 to 81 wherein the fine particle fractions measured in a MSLI (stages 3-5) are greater than about 20% or about 30%.

84. A pharmaceutical formulation according to any of claims 78 to 83 wherein the pulmonary formulation is used in a dry powder delivery device without any further formulation with larger carrier particles such as lactose.

85. A pharmaceutical formulation according to any of claims 78 to 84 wherein the emitted dose, fine particle fraction and mass median aerodynamic diameter are substantially unchanged following equilibration to a relative humidity of up to about 60% or up to about 80% followed by re-drying to the original weight.

86. A pharmaceutical formulation according to any of claims 78 to 85 wherein for pulmonary formulations, the particles have a mass median aerodynamic diameter less than about 10 microns, less than about 5 microns or less than about 3.5 microns.

87. A pharmaceutical formulation according to any of claims 78 to 86 wherein free-flowing, non-hygroscopic low static particles have a maximum cross-sectional diameters in the range of about 1-5 microns.

88. A pharmaceutical formulation according to any of claims 78 to 87 wherein the bioactive molecule coated particles have the form of high aspect ratio flakes which have mass median aerodynamic diameters smaller than their maximum cross-sectional diameters.

89. A pharmaceutical formulation according to claim 88 wherein the mass median aerodynamic diameters are substantially unchanged on exposure to high humidity such as about 80 - 90% humidity.

90. A pharmaceutical formulation according to any of claims 78 to 89 wherein pulmonary formulations are selected to have crystalline cores comprised of amino-acids such as valine, histidine, isoleucine, glycine or glutamine.

91. A pharmaceutical formulation according to claim 90 wherein the pulmonary formulations are selected from any of the following: a crystalline core of valine and a coating of a therapeutic protein such as insulin; a crystalline core of histidine and a coating of an enzyme; a crystalline core of valine and a coating of an enzyme inhibitor such as α-antitrypsin; a crystalline core of valine and a coating of DNA; a crystalline core of valine and a vaccine coating; and a crystalline core of glutamine and a vaccine coating; a crystalline core of glutamine and a coating of albumin.

92. A parenteral formulation comprising particles or suspensions of particles according to any of claims 1 to 36.

93. A parenteral formulation according to claim 92 wherein the parenteral formulations are delivered using intravenous, subcutaneous or intra-muscular injection or in sustained or controlled release formulations.

94. A sustained or controlled release pharmaceutical formulation (or a depots) comprising particles or suspensions of particles according to any of claims 1 to 36.

95. A sustained or controlled release pharmaceutical formulation according to claim 94 wherein substantially each of the particles is evenly coated or dispersed within a material which alters the release or delivery of the components of the particles.

96. A pulmonary drug delivery device comprising particles or a pharmaceutical formulation according to any of claims 1 to 91.

97. A pulmonary drug device according to claim 96 wherein the pulmonary drug delivery device is a liquid nebulizer, aerosol-based metered dose inhaler, dry powder dispersion device or multi-dose inhaler device.

98. Use of particles according to any of claims 1 to 36 in the manufacture of a medicament wherein the medicament is administered in a pulmonary, parenteral, nasal, sublingual, intravenous, rectal, vaginal, intra-anal or oral administration, for use in therapy.

99. Use of particles according to claim 98 for treating cancers, especially human cancers, including melanomas, skin cancer, lung cancer, breast cancer, colon cancer and other cancers; mumps; measles; rubella; flue; influenza; diptheria; tetanus; polio; pertussus; hepatitis A, B and C; HIV; rabies; and diabetes.